Decision Memo for Anticancer Chemotherapy for Colorectal Cancer (CAG-00179N)

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) will cover the use of oxaliplatin (Eloxatin™), irinotecan (Camptosar®), cetuximab (Erbitux™), or bevacizumab (Avastin™), in clinical trials identified by CMS and sponsored by the National Cancer Institute (NCI). The list of identified trials for which these drugs and other items and services that are covered appears in Appendix A and on the following CMS website: http://www.cms.hhs.gov/coverage/download/id90b.pdf[PDF, 1MB].

This decision does not modify the existing requirement for coverage of these and other anticancer chemotherapeutic agents for FDA-approved indications or for indications listed in an approved compendium.

This decision makes no change in coverage for any off-label uses of these drugs provided outside of the clinical trials identified in this decision memorandum. Contractors will continue to make coverage determinations for medically accepted uses of off-label indications based on guidance provided by the Secretary.

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Decision Memo

To: Administrative File #CAG-00179N
Anticancer Chemotherapy for Colorectal Cancer

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Subject: Coverage Decision Memorandum for Anticancer Chemotherapy for Colorectal Cancer
Date: January 28, 2005

I. Decision

The Centers for Medicare & Medicaid Services (CMS) will cover the use of oxaliplatin (Eloxatin™), irinotecan (Camptosar®), cetuximab (Erbitux™), or bevacizumab (Avastin™), in clinical trials identified by CMS and sponsored by the National Cancer Institute (NCI). The list of identified trials for which these drugs and other items and services that are covered appears in Appendix A and on the following CMS website: http://www.cms.hhs.gov/coverage.

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II. Background

Colorectal Cancer Epidemiology

As the second leading cause of cancer death in the United States, colorectal cancer accounts for about 10% of all cancer deaths. An estimated 146,940 new cases will be diagnosed and 56,730 deaths will occur in the United States in 2004. (American Cancer Society, 2004) The disease generally affects individuals older than 50 years, with a mean age of 72 years. Additional details regarding the incidence and prevalence of colorectal cancer are available from the SEER-Medicare database located on-line at http://www.seer.cancer.gov/.

Colorectal cancer is a heterogeneous disease resulting from a complex interaction between environmental and genetic factors. The National Cancer Institute (NCI) estimates that about 75% of colorectal cancer patients present with no apparent evidence of having inherited the disease. The remaining 25% of patients have a family history of colorectal cancer that suggests an inherited or acquired genetic contribution, common environmental exposures among family members, or a combination of both. There is strong epidemiological evidence that a personal history of colon adenomas increases the risk of developing colon cancer (Neugut, Jacobson, & DeVivo, 1993), and that adenomatous polyps are benign tumors that may undergo malignant transformation. The NCI, in a document entitled *Genetics of Colorectal Cancer*, provides a succinct review of the natural history, molecular biology, risk factors, interventions and prevention associated with colorectal cancer. The review is located online at: http://www.cancer.gov/cancertopics/pdq/genetics/colorectal

Colorectal Cancer Disease Process

The treatment of colorectal cancer is dependent on the stage of the disease at the time of diagnosis. If the disease is confined to the muscularis propria, as in stage I disease, surgical resection is frequently curative and additional therapies are not necessary. Stage II tumors represent a state where the primary tumor has advanced through the muscularis propria, but no disease is present in the regional lymph nodes or distant sites. Therapy of stage II disease consists of surgical resection. The use of adjuvant chemotherapy in stage II disease is controversial. Adjuvant chemotherapy is administered with the intent to improve outcome by eradicating any remaining microscopic collections of tumor cells not removed by surgical treatment of the primary colorectal cancer. If the tumor has spread to the regional lymph nodes but not to distant organs, stage III disease is present and therapy frequently consists of both surgical resection and adjuvant chemotherapy. Patients with detectable metastases to distant organs have stage IV disease and are candidates for chemotherapy. First-line chemotherapy refers to the treatment of patients with metastatic disease who, with the possible exception of adjuvant chemotherapy, have not yet received chemotherapy. Once first-line chemotherapy is started, the patient is monitored to determine if the disease regresses or stabilizes. If the patient's disease relapses or spreads, the first-line chemotherapy protocol is no longer active and a new drug regimen may be introduced. These modified regimens are referred to as second-line chemotherapy. Refer to the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Sixth Edition* (2002) for a detailed description of colon cancer staging or visit www.cancerstaging.net for more information.

Chemotherapy Treatment Options

Chemotherapy has been used in both the adjuvant and advanced disease settings. The following table summarizes the prevalence, prognosis, and role of chemotherapy in colorectal cancer by stage. (Haller 2003, Engstrom 1996)

Colorectal Cancer			
Stage	**Patients at Diagnosis (%)**	**Approximate 5-Year Survival (%)**	**Role of Chemotherapy**
I	24	> 80	None
II	26	75 to 80	Adjuvant (use is controversial)

Colorectal Cancer			
Stage	**Patients at Diagnosis (%)**	**Approximate 5-Year Survival (%)**	**Role of Chemotherapy**
III	29	50 to 75	Adjuvant
IV	22	< 5	First and Second-line

The National Institutes of Health Consensus Conference (NIH, 1990) recommended the adoption of a fluorouracil-levamisole regimen for use in the adjuvant setting contributing to the rapid adoption of adjuvant therapy throughout the United States. Active clinical research continued during the 1990s as other fluorouracil-based protocols were tested. These protocols included various dosing schedules, as well as using leucovorin in place of levamisole. Based on these trials, the adjuvant protocols combining fluorouracil with leucovorin (5-FU/LV) evolved to be the standard of care (Chau & Cunningham, 2002).

The potential role of adjuvant chemotherapy with 5-FU based regimens in stage III (and to a lesser extent stage II) disease has been the focus of a series of large randomized studies sponsored by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and National Cancer Institute co-operative trials. These trials established the benefits of adjuvant therapy in stage III disease, indicating an increase in disease free 5-year survival in the range of 20% to 30%, with 5-year survivals approaching 60% to 65% (Chau & Cunningham, 2002; Rao & Cunningham, 2003).

Paradoxically, despite disproportionate proven benefits in long-term survival in adjuvant therapy, drug approvals for colorectal cancer have usually centered on the treatment of advanced disease. Drugs are usually introduced to clinical trial as second-line therapies for patients who no longer respond to current first-line therapies. If a favorable response is measured, the drug may then be tested as first-line therapy and ultimately in the adjuvant setting. Adjuvant trials are also difficult, as patients must be followed for a far longer period than patients with more advanced disease to reach useful endpoints. However, a generally accepted principle of adjuvant therapy requires the drug to first demonstrate activity in the metastatic setting.

Chemotherapy for advanced colorectal disease currently includes 5-FU/LV, capecitabine (Xeloda®), oxaliplatin, irinotecan, cetuximab, and bevacizumab used as single agents and in combination chemotherapeutic regimens. 5-FU and capecitabine are not subjects of this national coverage determination review. However, information on the evolution of 5-FU therapy including how it compares to best supporting care, and its use with other agents such as leucovorin, can be found online at the FDA website: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3592b1a.pdf. Capecitabine, an oral prodrug of 5'-deoxy-5-flourocytidine, is converted to 5-FU in tumor tissue. (A prodrug is an inactive form of a drug that exerts its effects after metabolic processes within the body convert it to a usable or active form.) Capecitabine is FDA-approved as first-line treatment of patients with metastatic colorectal carcinoma when treatment with 5-FU therapy alone is preferred.

Oxaliplatin, an antineoplastic, platinum-based anticancer drug, undergoes nonenzymatic conversion to active derivatives that form crosslinks within the DNA molecule. This crosslinking interferes with DNA replication. Irinotecan, an antineoplastic agent, is a type I DNA topoisomerase inhibitor. DNA topoisomerases are enzymes in the cell nucleus that regulate DNA topology and facilitate nuclear processes such as DNA replication, recombination, and repair. Cetuximab, a recombinant human monoclonal antibody, binds specifically to the epidermal growth factor receptors (EGFR) sites on tumor cells, and blocks ligand-induced phosphorylation of EGFR, resulting in inhibition of cell growth. Bevacizumab, also a recombinant humanized monoclonal antibody, binds to the natural protein, human vascular endothelial growth factor (VEGF), and prevents interaction of VEGF with its receptors on the surface of endothelial cells. When VEGF is targeted and bound to bevacizumab, it cannot stimulate the growth of blood vessels, thus denying tumors blood, oxygen and other nutrients needed for growth. By inhibiting angiogenesis, bevacizumab may reduce microvascular growth of tumors and inhibit metastatic disease progression.

Clinical Trials

Under the current Medicare clinical trial policy (National Coverage Determinations Manual, section 310.1), the routine costs of a qualified clinical trial are provided in either the experimental or the control arms of a clinical trial, unless the routine items or services:

- do not exist within a Medicare benefit category,
- are statutorily excluded from coverage,
- are non-covered through a national coverage determination,
- are provided solely to satisfy data collection and analysis needs, and are not used in the direct clinical management of the patient,
- are the investigational item or service, itself, or
- are customarily provided by the research sponsors free of charge for any enrollee in the trial.

In general, Medicare coverage of the cost of anti-cancer drugs in clinical trials for off-label indications is determined by local contractors. Routine costs incurred in the clinical trial are paid. The CMS clinical trial policy is located online at: http://www.cms.hhs.gov/manuals/103_cov_determ/ncd103index.asp

III. History of Medicare Coverage

An item or service is covered by Medicare Part A or Part B if it falls into one or more benefit categories, and is not otherwise excluded by statute from coverage. Medicare has provided reimbursement for anti-cancer chemotherapy in a clinical setting when used in accordance with FDA-approved labeling. Under §1861(b) of the statute, anti-cancer chemotherapeutics, such as oxaliplatin, irinotecan, cetuximab, and bevacizumab, are covered as a Part A benefit when administered in an inpatient hospital setting. If the Medicare contractors determine that agents are not usually self-administered, they are covered as a Medicare Part B benefit under §1861(s)(2)(A) when administered in a physician's office or outpatient setting, and under §1861(s)(2)(B) when administered in an outpatient hospital setting.

The addition of §1861(t)(2)(B) to the Social Security Act provided reimbursement for off-label uses of FDA approved drugs and biologicals used in an anti-cancer chemotherapeutic regimen under specific circumstances as described below.

Section 1861(t)(2) of the Social Security Act:

(A) For purposes of paragraph (1), the term "drugs" also includes any drugs or biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication (as described in subparagraph (B)).

(B) In subparagraph (A), the term "medically accepted indication", with respect to the use of a drug, includes any use which has been approved by the Food and Drug Administration for the drug, and includes another use of the drug if—

(i) the drug has been approved by the Food and Drug Administration; and

(I) such use is supported by one or more citations which are included (or approved for inclusion) in one or more of the following compendia: the American Hospital Formulary Service-Drug Information, the American Medical Association Drug Evaluations, the United States Pharmacopoeia-Drug Information, and other authoritative compendia as identified by the Secretary, unless the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia, or

(II) the carrier involved determines, based upon guidance provided by the Secretary to carriers for determining accepted uses of drugs, that such use is medically accepted based on supportive clinical evidence in peer reviewed medical literature appearing in publications which have been identified for purposes of this subclause by the Secretary.

The Secretary may revise the list of compendia in clause (ii)(I) as is appropriate for identifying medically accepted indications for drugs. (42 U.S.C. § 1395x(t)(2)).[1]

Effective January 1, 1994, the Health Care Financing Administration (now CMS) implemented a change in policy in response to the addition of §1861(t)(2). HCFA published contractor guidance in the Carriers Manual, part 3, section 2049 (now the Medicare Benefit Policy Manual, chapter 15, section 50) for unlabeled indications of FDA approved drugs and biologicals used in anti-cancer chemotherapeutic regimens for medically accepted indications. The Medicare Benefit Policy Manual is located online at: http://www.cms.hhs.gov/manuals/102_policy/bp102index.asp

Also effective January 1, 1994, by authority of §1861(s)(2)(Q), HCFA extended coverage under specified conditions to prescribed oral anti-cancer drugs that are versions of covered non-self-administrable chemotherapeutic agents. The oral drug must have the same active ingredients as the covered non-self administrable anti-cancer drug or biological that it replaces, must be furnished incident to a physician's service, and must be used for the same indications (including unlabeled uses) as the drug it replaces. Effective January 1, 1999, CMS expanded coverage of oral anti-cancer drugs to include FDA-approved prodrugs used to replace the covered non-self-administrable version of the drug. A prodrug may have a different chemical composition than the non-self-administrable version of the drug it replaces but metabolizes into the same chemical composition in the body.

On February 12, 2003, CMS initiated a national coverage determination for oxaliplatin to examine appropriate use in the Medicare program. After internal review and analysis of public comments, CMS decided to add irinotecan to the NCD review on May 2, 2003. On September 1, 2004, CMS modified the NCD review to include consideration of off-label uses of oxaliplatin, irinotecan, bevacizumab, and cetuximab that are not listed as indicated in one or more of the major drug compendia cited in §1861(t)(2)(B)(ii)(I) of the statute.

CMS and the National Cancer Institute (NCI), the federal government's principal agency for cancer research and training, entered into discussions to explain how the two agencies can align their resources to accelerate the development of evidence for emerging cancer treatment regimens. Through these discussions the approach linking coverage to participants in clinical trials was developed.

IV. Timeline of Recent Activities

February 12, 2003	CMS opened a national coverage determination (NCD) review of oxaliplatin for colorectal cancer based on an internally generated request to evaluate when the use of oxaliplatin is reasonable and necessary in the Medicare population.
May 2, 2003	CMS added irinotecan to the NCD review. CMS extended the public comment period by 30 days.
June 3, 2003	CMS accepted a formal request to extend the public comment period six weeks to enable the manufacturer to submit detailed information for irinotecan. In addition, CMS invited public comment on off-label, adjuvant use of the drugs.
August 18, 2003	CMS held multiple meetings with industry representatives and consulted with public and private sector experts. Substantive information on off-label uses of the drugs was reviewed, including but not limited to first-line therapy for oxaliplatin, and adjuvant therapy for both oxaliplatin and irinotecan. CMS also modified the title of the national coverage analysis to reflect the current scope of review.
November 17, 2003	CMS met with industry representatives to further discuss emerging data on off-label uses of oxaliplatin and irinotecan.
January 9, 2004	The FDA announced approval of oxaliplatin in combination with infusional 5-fluorouracil and leucovorin for the treatment of patients previously untreated for advanced colorectal cancer.
January 29, 2004	CMS extended the NCD due date to allow time for internal review and clearance.
February 12, 2004	The FDA announced approval of cetuximab, used either in combination with irinotecan or alone in patients who can not tolerate irinotecan, for the treatment of patients with colorectal cancer that has spread to other parts of the body, i.e., metastatic colorectal cancer.
February 26, 2004	The FDA announced approval of bevacizumab, used in combination with intravenous 5-fluorouracil-based chemotherapy, as a first-line treatment for patients with metastatic colorectal cancer.
September 1, 2004	

CMS modified the NCD review to include consideration of off-label uses of oxaliplatin, irinotecan, bevacizumab, and cetuximab that are not listed as indicated in one or more of the major drug compendia cited in §1861(t)(2)(B)(ii)(I) of the statute.

The title of the national coverage analysis was modified to reflect the current scope of review.

September 15, 2004	CMS met with the National Cancer Institute to discuss clinical and scientific issues including identification of high-priority clinical questions and collection of evidence about the optimal use of oxaliplatin, irinotecan, bevacizumab, and cetuximab.
November 1, 2004	CMS published the proposed national coverage determination memorandum and solicited public comments on the decision memorandum, the trials recommended for coverage, the process for selecting future trials, and the process contractors use to approve off-labeled use of anticancer drugs.
November 19, 2004	To accommodate requests for extension of the public comment period, the due date of 11/30/04 was extended 30 days.
December 31, 2004	Public comment period ended

V. FDA Status

Oxaliplatin

On August 9, 2002, the FDA approved the New Drug Application (NDA) for accelerated approval of oxaliplatin in combination with infusional 5-FU/LV for the second-line treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within six months of completion of first-line therapy with the combination of bolus 5-FU/LV and irinotecan (Rothenberg et al., 2003). On January 9, 2004, the FDA approved the supplemental NDA for accelerated approval of oxaliplatin in combination with infusional 5-FU/LV for first-line therapy of metastatic carcinoma of the colon or rectum. The FDA's review of the data showed that, compared to the standard treatment (irinotecan plus 5-FU/LV), the oxaliplatin 5-FU/LV regimen was superior in survival, in shrinking tumors, and in delaying tumor regrowth. Approval was expedited through the FDA Fast Track program. Information on the FDA Fast Track and Accelerated Approval programs is found online at: http://www.fda.gov

On November 4, 2004, the FDA approved oxaliplatin for use in combination with infusional 5-FU/LV, for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. The indication is based on an improvement in disease-free survival, with no demonstrated benefit in overall survival after a median follow up of 4 years. (Food and Drug Administration, 2005)

Irinotecan

On October 22, 1998, irinotecan received FDA accelerated approval for second-line treatment of metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU based therapy. On April 20, 2000, irinotecan received FDA approval for first-line treatment in combination with 5-FU/LV of metastatic carcinoma of the colon or rectum. On May 10, 2002 Pharmacia Corp, manufacturer of irinotecan, issued a Dear Healthcare Professional letter indicating that the prescribing information contained in the “Boxed Warning, Warnings and Precautions” sections of the FDA label were revised to identify patients at higher risk of severe toxicity, to clarify dose modification guidelines, and to augment information about management of treatment-related toxicities, including severe and occasionally life-threatening diarrhea. The labeling changes for irinotecan arose following the recommendations made at a December 6, 2001 meeting of the FDA Oncologic Drugs Advisory Committee (ODAC). This committee was convened to review all available safety data for the combination regimen of irinotecan plus bolus 5-FU/LV. Consistent with ODAC's unanimous conclusions, the FDA agreed that both the bolus and the infusional regimens of irinotecan plus 5-FU/LV regimens for the first-line treatment of patients with metastatic colorectal cancer, and the starting dose and schedule for both regimens, remain unchanged on the revised label. (Food and Drug Administration, 2005)

Cetuximab

On February 12, 2004, cetuximab received FDA accelerated approval for use, in combination with irinotecan, for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer in patients who are refractory to irinotecan-based chemotherapy. Cetuximab was also approved as a single agent for the treatment of EGFR-expressing, metastatic colorectal cancer in patients who are intolerant to irinotecan-based chemotherapy. The effectiveness of cetuximab is based on objective response rates. No data are available that demonstrate an improvement in disease related symptoms or increased survival with cetuximab. Approval was expedited through the FDA Fast Track program. (Food and Drug Administration, 2005)

Bevacizumab

On February 26, 2004, the FDA approved bevacizumab, in combination with intravenous 5-FU-based chemotherapy, for the first line treatment of patients with metastatic carcinoma of the colon or rectum. Approval was expedited through the FDA Fast Track program. On August 12, 2004, the FDA and Genentech Inc., manufacturer of bevacizumab, issued a Dear Healthcare Provider letter stating that there is evidence of an increased risk of serious arterial thromboembolic events, including cerebrovascular accident, myocardial infarctions, transient ischemic attacks, and angina related to use of bevacizumab. The risk of fatal arterial thrombotic events is also increased. (Food and Drug Administration, 2005)

VI. General Methodological Principles of Study Design

When making national coverage determinations under 1862(a)(1)(A) of the Social Security Act, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. The *General Methodological Principles of Study Design* is located in Appendix B.

VII. Evidence

Introduction

Consistent findings across studies of net health outcomes associated with an intervention or diagnostic test as well as the magnitude of its risk and benefits are key to the coverage determination process.

1. Sources of Evidence

CMS reviewed the published clinical evidence on uses of oxaliplatin, irinotecan, cetuximab, and bevacizumab. The published literature was searched using the Entrez-PubMed database of the National Library of Medicine. Key words included combinations of the following terms “Eloxatin, Camptosar, Erbitux, Avastin, oxaliplatin, irinotecan, cetuximab, bevacizumab, capecitabine, colorectal, colon, clinical trial, rectal, (with or without) adjuvant”. The literature for these drugs was also surveyed by running searches using the key words “oxaliplatin” or “irinotecan” in combination with a limit on the article type set to “clinical trial”. Searches were also performed using the key phrases “oxaliplatin not colorectal”, “irinotecan not colorectal”, “cetuximab not colorectal, and “bevacizumab not colorectal” limited to “clinical trials”. Review articles and references were also obtained and used to survey the field for relevant clinical trial data. In meetings with industry, other relevant abstracts and articles were received and reviewed.

In addition to the directly relevant clinical trial data, CMS actively sought the opinion of oncology experts from both the public and private sectors, including governmental agencies, educational institutions, and the pharmaceutical industry. Public comments from practicing physicians, cancer advocacy groups, and beneficiaries were considered.

2. Health Outcomes

Treatment of colorectal cancer is dependent on the stage of the disease at diagnosis. It is important to consider that when used in the metastatic disease setting, chemotherapy may result in increased overall survival (OS) typically measured in months. Overall survival compares the median lifespan of the experimental subjects enrolled in each arm of a study. Often in the metastatic setting, other criteria such as objective response rate (OR) or progression free survival (PFS) are used. These criteria involve measuring a subject’s malignant disease burden typically by radiological methods. If the tumor burden is noted to decrease by a specified amount (for example a 50% or greater reduction in the maximal diameter of detectable metastasis) an OR has occurred. Alternatively, if the measured disease burden does not increase over a period of time, an increase in PFS may have occurred. While neither of these criteria is as stringent as OS, it is generally agreed that a correlation exists between these criteria (Ragnhammar et al., 2001; Buyse et al., 1996; Graf et al., 1994).

Discussion of Evidence Reviewed

1. External Technology Assessment

An external technology assessment was not performed in conjunction with the NCD review.

2. Internal Technology Assessment

Peer-Reviewed Literature for Off-Label Colorectal Cancer Indications

Our review indicated that there are no studies of off-label use of oxaliplatin, irinotecan, cetuximab, and bevacizumab for the treatment of colorectal cancer appearing in a peer-reviewed publication. The proposed Decision Memorandum described the **M**ulticenter **I**nternational **S**tudy of **O**xaliplatin/5FU-LV in the **A**djuvant Treatment of **C**olon Cancer (MOSAIC) as the only study of off-label use for colorectal cancer appearing in a peer-reviewed publication. This trial has been completed and oxaliplatin is FDA approved for use in adjuvant treatment of colon cancer.

Peer-Reviewed Literature for Off-Label Non-Colorectal Cancer Indications

The availability of published peer-reviewed medical literature for off-label uses of oxaliplatin, irinotecan, cetuximab, and bevacizumab for the treatment of cancer is shown in the table below. Our brief review of this literature found evidence that ranged in quality.

Published Clinical Trial Activity
(X = Yes)

Cancer	Oxaliplatin	Irinotecan	Cetuximab	Bevacizumab
Biliary	X	X		
Breast	X	X		X
Cervical	X	X		
Esophageal	X	X		
Gastric	X	X		
Non-Hodgkin's Lymphoma	X	X		X
Non-small Cell Lung Carcinoma	X	X	X	X

Cancer	Oxaliplatin	Irinotecan	Cetuximab	Bevacizumab
Ovarian	X	X		
Pancreatic Cancer	X	X	X	
Prostate	X	X		
Renal Cell Carcinoma	X	X	X	X
Transitional Cell Carcinoma	X	X		
Small-cell Lung Carcinoma		X		

3. Medicare Coverage Advisory Committee

A Medicare Coverage Advisory Committee (MCAC) meeting was not convened for this review.

4. Evidence-Based guidelines

Citations from the drug compendia identified in §1861(t)(2)(B)(ii)(II) of the statute, the American Hospital Formulary Service-Drug Information (AHFS-DI) and the United States Pharmacopoeia-Drug Information (USP-DI), support the FDA indications for these four agents. When reviewing 2004 authorized compendia (AHFS-DI and USP-DI) for indications of these agents, they are essentially consistent. In both texts cetuximab is indicated as second line for the treatment of EGFR-expressing, metastatic colorectal cancer in patients who are intolerant/refractory to irinotecan-based therapy, both as mono-therapy and in combination with irinotecan. Both sources also note that irinotecan is indicated for first line therapy in combination with regimens that include 5FU/leucovorin for metastatic colorectal cancer, and second line mono-therapy for metastatic colorectal cancer following first line chemotherapy with 5-FU.

Though the 2004 USP-DI does not list bevacizumab (no 2005 monogram available yet), the AHFS-DI has established it as an indication for first line therapy in combination with 5-FU based chemotherapy for metastatic colorectal carcinoma. Oxaliplatin is also listed as indicated for both first line and second line agents for metastatic colorectal carcinoma in combination with 5FU/leucovorin in the USP-DI, (for USP-DI capecitabine can be substituted for 5FU/leucovorin). AHFS-DI also lists oxaliplatin as a second line agent for metastatic colorectal carcinoma in combination with 5FU/leucovorin, but lists oxaliplatin, used in combination with 5FU/leucovorin, as an indication for the treatment of advanced carcinoma of the colon or rectum. The compendia should be consulted directly as information regarding drug usage changes as new evidence becomes available.

The National Comprehensive Cancer Network (NCCN) publishes clinical practice guidelines for both colon cancer and rectal cancer that discuss generally accepted treatment protocols. These documents also contain a detailed description of the current *American Joint Committee of Cancer Staging Manual 6th Edition* published in 2002. These guidelines recommend consideration of oxaliplatin and irinotecan in Stage IV or salvage therapy in colorectal cancer. Irinotecan is also mentioned as a promising agent in non-small cell lung cancer. Cetuximab is recommended for consideration (with or without irinotecan) as second-line therapy for colon cancer. Bevacizumab (in combination with 5-FU based chemotherapy) is recommended for consideration as first line therapy for colon cancer. The NCCN guidelines encourage participation in clinical trials stating that clinical trials provide the best management for any cancer patient. (NCCN, 2004)

5. Professional Society Position Statements

The American Society of Clinical Oncology (ASCO) does not recommend the routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer. However, ASCO notes that there are populations of patients with stage II disease that could be considered for adjuvant therapy, including patients with inadequately sampled nodes, T4 lesions, perforation, or poorly differentiated histology. (ASCO 2004)

6. Expert Opinion

CMS met with representatives for Sanofi Synthelabo, Inc., Pfizer, Bristol-Myers Squibb Co., and Genentech, manufacturers of oxaliplatin, irinotecan, cetuximab, and bevacizumab respectively, to discuss evidence present for these chemotherapeutic agents. During the course of this review CMS consulted with staff from the FDA and NCI to discuss clinical and scientific issues including identification of high-priority clinical questions and collection of evidence about the optimal use of oxaliplatin, irinotecan, bevacizumab, and cetuximab.

7. Public Comments

Initial Comment Period: March 2003 - July 2003

CMS received a total of 95 letters during the public comment periods. Fifty-eight of these letters were from medical oncologists representing private practices, group practices, and cancer centers across the country. Several of these physicians have clinical trial experience. CMS received 17 letters from Congressional and state elected officials. Several letters were received from representatives of cancer advocacy groups, including the Abigail Alliance for Better Access to Developmental Drugs, Alliance for Aging Research, Cancer Leadership Council, Cancer Research and Prevention Foundation, Colon Cancer Alliance, Colorectal Cancer Network, EyesOnThePrize.org, Marti Nelson Cancer Foundation, National Coalition for Cancer Survivorship, National Surgical Adjuvant Breast and Bowel Project (NASBP) Foundation Inc., and Stop Colon/Rectal Cancer Foundation. CMS also received letters from the American Society of Clinical Oncology, drug industry representatives and two beneficiaries. Several of the commenters provided supplemental information and offered follow-up contact.

Comments are summarized below:

- Adjuvant therapy provides an unmet need for those patients whose physician has determined the treatment clinically indicated and desirable.
- Recent clinical studies report an increased overall survival and improved quality of life with use of oxaliplatin for first-line colorectal cancer therapy.
- A noncoverage determination for oxaliplatin and irinotecan for off-label use in treatment of colorectal cancer would limit patient access to care.
- A noncoverage determination for off-label use would hinder research and discovery of new advances in colorectal chemotherapy.
- The costs of therapy for oxaliplatin and irinotecan are comparable.
- CMS lacks the legal authority to noncover off-label uses of anti-cancer chemotherapy drugs.

Final Comment Period: November 1, 2004 – December 31, 2004

In response to the publication of the proposed national coverage determination memorandum on November 1, 2004, we received comments from 10 individuals and groups during the required 30-day statutory period, including four requests to extend the comment period an additional 30 days through December 31, 2004. We granted the request for comment period extension and received an additional 17 comments. Commenters included national professional associations, national associations of cancer centers, biotechnical and pharmaceutical companies, cancer patient advocacy groups, and other individuals including caregivers and cancer patients.

The majority of commenters commended CMS for the decision to expand patient access to anti-cancer chemotherapy while improving the evidentiary basis for coverage through enrollment in clinical trials. However some commenters stated that the proposal is not an expansion in coverage and should be withdrawn since sponsors often donate oncology-studied drugs. In general, the commenters predominantly expressed concerns related to 1) clinical trial selection and design, 2) potential unintended consequences of coverage decision 3) perception of restricting contractor discretion, and 4) choice of an NCD for launching major changes in coverage requirements. Many commenters provided recommendations to questions posed by CMS in the proposed NCD.

On the issue of trial selection, commenters felt that the proposed NCD left too many unanswered questions regarding trial selection criteria and design to allow full endorsement; that the nine NCI-sponsored trials are too limited in scope and number; and that covering drugs for only NCI-sponsored trials could potentially decrease accruals to trials at non-NCI sites such as comprehensive cancer centers. While CMS recognizes that the complete details of the selected trials will not be available until the protocols are final, we believe that sufficient information is available to determine that these are appropriate trials for CMS to cover. We also recognize that a more detailed process is necessary for selecting future trials and will work with industry and other stakeholders to define that process.

The observations on the potential unintended consequences of this decision included:

- Beneficiaries who do not meet the requirements of the protocols would be unable to enroll;
- Beneficiaries may have increased out-of-pocket costs for participating in clinical trials than they would have if the parameters of clinical trial funding were left to negotiation between sponsors, investigators and manufacturers as is currently the case;
- The proposal creates a danger of replacing industry clinical trial support with public funding;
- A beneficiary who is a potential participant in two competing clinical trials and one of those trials is covered by Medicare and the drug product is provided free-of-charge by the drug sponsor in the other study, the beneficiary is likely to be steered toward the trial where the drug is provided for free, creating the potential for enrollment to be skewed due to financial considerations.

The basic requirements for enrollment in a trial do not change with this NCD and adding payment for drugs will not change the potential of a beneficiary to enroll in the trial. We also do not expect industry to discontinue the common practice of providing drugs in clinical trials. This NCD is to ensure that clinical trials in which industry does not provide the drugs will be available to the Medicare beneficiary.

Several commenters felt that the proposed NCD left the perception that contractor discretion for other off-labeled use of these drugs would be restricted. We are clarifying that contractors will continue to follow appropriate guidelines for all other uses of these drugs.

Finally, several commenters felt that the NCD was not the appropriate vehicle for developing major changes in coverage requirements. While CMS believes that the authority in Section 1871 of the Social Security Act allows the use of the NCD process to develop coverage policy, and that the NCD process allows for public comment and input, we do plan to rapidly engage the public in defining a more detailed process for selecting future trials.

VIII. CMS Analysis

National coverage determinations are made with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act. § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not otherwise be excluded from coverage. Moreover, with limited exceptions, no payment may be made for any expenses incurred for items or services that are not "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member[.]" § 1862(a)(1)(A).

Under authority of §1861(t)(2) of the statute, Medicare provides coverage for FDA-approved indications for anticancer chemotherapeutic agents and for other indications that are listed in specific approved compendia (see History of Medicare Coverage under Section II. Background). Under authority of §1861(t)(2)(B)(ii)(I) of the statute, uses not approved by the FDA and listed as not indicated in one or more of the cited compendia are generally noncovered. Medicare contractors, based on guidance provided by CMS, may determine local coverage policy for off-label indications for an FDA-approved anticancer chemotherapeutic agent if they find supporting clinical evidence in peer-reviewed medical literature.

Summary of Medicare Covered Colorectal Indications

Agent	Adjuvant	1st Line	2nd Line
Oxaliplatin	FDA	FDA/Compendia	FDA/Compendia
Irinotecan	*	FDA/Compendia	FDA/Compendia
Cetuximab	*	*	FDA/Compendia
Bevacizumab	*	FDA/Compendia	*

* No published peer-reviewed literature.

As the table above indicates, oxaliplatin, irinotecan, cetuximab, and bevacizumab are Medicare covered for the FDA-approved and compendia-supported use in adjuvant and/or 1st and/or 2nd line treatment of advanced colorectal cancer.

The off-label use of irinotecan for the treatment of non-small cell lung cancer is supported in one of the approved drug compendia; therefore this off-label use is covered by Medicare. No other off-label use for irinotecan, oxaliplatin, cetuximab, or bevacizumab appears as supported in the approved drug compendia. Off-label coverage of these agents is therefore determined by the Medicare contractors based on their review of the medical literature. During our NCD review of the medical literature, we found studies of off-label indications for these agents that varied widely in quality.

Increased understanding of the biology of cancer and emerging technologies is making possible new approaches in treating cancer. To ensure that beneficiaries have access to the most appropriate cancer treatments, it is imperative that adequate clinical trial data for off-label uses be made available to patients and providers for clinical decision-making and to policymakers.

At the request of CMS, NCI identified high priority clinical trials studying off-label uses of the four agents that are the subject of this national coverage determination review. It was agreed that the selected trials should address questions likely to lead to important changes in therapy and that by covering the use of these agents in selected trials; we will:

- offer consistent national coverage for these specific trials,
- ensure continued advancement in knowledge for the appropriate use of these agents,
- accelerate the development of evidence for new or emerging cancer treatment regimens for these agents
- ensure beneficiaries rapid access to promising new uses of approved technologies under controlled clinical trial conditions,
- serve as a potential model for additional coverage expansions in clinical trials for other anti-cancer chemotherapeutic agents.
- encourage industry to invest in studies that will expand knowledge base for patient and doctor discussions.

Although we do not find sufficient evidence to support coverage of off-label use of cancer chemotherapy for all persons who have cancer, a sufficient inference of benefit can be drawn to support limited coverage in the context of an NCI-sponsored clinical trial that provides rigorous safeguards for patients. We base this inference on the evidence discussed above regarding the benefits of chemotherapy for labeled uses. We further believe that NCI-sponsored clinical trials offer safeguards for patients to ensure appropriate patient evaluation and selection and reasonable use of cancer chemotherapy. We conclude that coverage for the off-label use of cancer chemotherapy could provide clinical benefits to Medicare beneficiaries with cancer, and that those benefits are likely to be present in the context of a clinical trial that assures informed individualized analysis and evaluation of the response to chemotherapy and patient health status, as well as an adequate plan for data and safety monitoring. The list and description of selected trials which we are covering is located in Appendix A and online at the following CMS website: http://www.cms.hhs.gov/coverage/download/id90b.pdf [PDF, 1MB].

The policy does not obviate the need for contractors to continue to review the medical literature and determine the conditions under which off-label indications of FDA-approved drugs and biologicals used in anti-cancer chemotherapeutic regimens for medically accepted indications are reasonable and necessary (SSA 1861(t)(2)(B)(ii)(II)). Contractors will not infer from this NCD that any other uses of these drugs should not be approved.

This policy also does not withdraw Medicare coverage for items and services that may be covered according to the existing national coverage policy for Routine Costs in a Clinical Trial (National Coverage Determination Manual, section 310.1). Routine costs will continue to be covered as well as other items and services provided as a result of coverage of these specific trials in this NCD. Specific reimbursements will be determined as the protocols are completed and the trials begin.

In addition to covering these specific NCI trials, we are interested in establishing other processes to identify appropriate trials for which we may provide coverage. We are also interested in identifying additional means of gathering evidence outside of a clinical trial setting for use in decision-making such as registries and analyses of routinely collected electronic data. Therefore, we will shortly begin a process to develop appropriate guidance (Medicare Modernization Act Section 731) that will include an Open Door Forum and will result in the publication of a draft guidance document. We encourage broad public participation in this process.

IX. Conclusion

The Centers for Medicare & Medicaid Services (CMS) will cover the use of oxaliplatin (Eloxatin™), irinotecan (Camptosar®), cetuximab (Erbitux™), or bevacizumab (Avastin™), in clinical trials identified by CMS and sponsored by the National Cancer Institute (NCI). The list of identified trials for which these drugs and other items and services that are covered appears in Appendix A and on the following CMS website: http://www.cms.hhs.gov/coverage.

This decision does not modify the existing requirement for coverage of these and other anticancer chemotherapeutic agents for FDA-approved indications or for indications listed in an approved compendium.

This decision makes no change in coverage for any off-label uses of these drugs provided outside of the clinical trials identified in this decision memorandum. Contractors will continue to make coverage determinations for medically accepted uses of off-label indications based on guidance provided by the Secretary.

APPENDIX A

Coverage of Anti-Cancer Drugs for Off-Label Indications in Selected NCI Clinical Trials

Updated List of Clinical Trials [PDF, 1MB]

The Centers for Medicare & Medicaid Services (CMS) is expanding coverage for Medicare beneficiaries by requiring national coverage for certain anticancer drugs in National Cancer Institute (NCI) sponsored trials. CMS will cover the studied drug and routine costs of the trials using the following anticancer drugs: oxaliplatin (Eloxatin™), irinotecan (Camptosar®), bevacizumab (Avastin™), and Cetuximab (Erbitux™). Consult the following NCI web page for details of the trials: http://www.cancer.gov/clinicaltrials

- **6660** is a two-phase study:

  Phase I will determine MTD and DLT evaluating the use of bevacizumab in carcinoma of the GI tract, breast, and ovary. It compares the use of capecitabine, irinotecan and bevacizumab; with capecitabine, oxaliplatin and bevacizumab.

  Phase II is a first-line treatment of metastatic colorectal cancer. Use MTD from phase I portion of the trial in patients with locally advanced or metastatic colorectal cancer.

- **C80405** is a phase III, first-line metastatic colorectal cancer trial. It consists of multiple arms: FOLFOX, FOLFIRI, CAPOX, or CAPIRI plus bevacizumab; FOLFOX, FOLFIRI, CAPOX, or CAPIRI plus cetuximab; and FOLFOX, FOLFIRI, CAPOX, or CAPIRI plus both bevacizumab and cetuximab.

- **E2204** is a phase II trial evaluating bevacizumab in an adjuvant setting for the treatment of pancreatic cancer. This study consists of 4 arms: surgery plus bevacizumab; surgery plus cetuximab; cetuximab plus gemcitabine, capecitabine and radiation treatment; and bevacizumab plus gemcitabine, with capecitabine and radiation treatment.

- **E3201** is a phase III clinical trial for patients with rectal cancer in an adjuvant setting. The trial design consists of four arms: 5-FU/LV (or FOLFIRI); 5-FU/LV (or FOLFIRI) plus bevacizumab; FOLFOX; or FOLFOX plus bevacizumab.

- **E4203** is a phase II, first line therapy for metastatic colorectal cancer study based on tumor thymidylate synthase expression in previously untreated patients with metastatic colon cancer. The study consists of two arms, comparing patients treated with irinotecan, oxaliplatin, and bevacizumab with patients treated with oxaliplatin and bevacizumab.

- **E5202** is a phase III clinical trial using bevacizumab in an adjuvant setting for patients with colon cancer. Molecular markers on tumors are used to place stage II patients in high or low risk categories. The low risk patients are observed, the high-risk patients are randomized to MFOLFOX6 + or – bevacizumab (treatment arms are identical to NSABP C-08).

- **RTOG-H0429** is a phase III trial evaluating the use of cetuximab in head and neck cancers. This study compares the use of AFX-CB or IMRT plus cetuximab and CDDP to AFX-CB or IMRT plus CDDP.

- **NSABP R-04** is for rectal cancer adjuvant setting for patients with stage II/III disease. The design consist of 2 arms: radiation with capecitabine +/- oxaliplatin, and the other arm consists of radiation with 5-FU CVI +/- oxaliplatin.

- **SWOG 0502** is a phase II clinical trial assessing two dose levels of bevacizumab, combined with imatinib, in patients with advanced, incurable gastrointestinal stromal tumors.

Abbreviations

5-FU -5-fluorouracil
5-FU/LV- 5-fluorouracil, leucovorin
AFX-CB - accelerated radiation by delayed concomitant boost
CAPIRI – capecitabine, irinotecan
CAPOX – capecitabine, oxaliplatin, 5-fluorouracil, leucovorin
CDDP – cisplatin
CVI - continuous intravenous infusion
DLT – dose limiting toxicity
FOLFIRI – oxaliplatin, 5-FU/LV, irinotecan
FOLFOX - oxaliplatin, 5-fluorouracil, leucovorin
IMRT - intensity-modulated radiation therapy
MFOLFOX6 – six-month regimen of oxaliplatin, 5-fluorouracil, leucovorin
MTD – minimum therapeutic dose
NSABP National Surgical Adjuvant Breast and Bowel Project
RTOG -Radiation Therapy Oncology Group
SWOG - Southwest Oncology Group

APPENDIX B

General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. The goal of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

An intervention is not reasonable and necessary if its risks outweigh its benefits. Among other things, CMS considers whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

[1] *The American Medical Association Drug Evaluations*, listed in §1861(t)(2)(B)(ii)(II) of the statute, is no longer in print.

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